EXHIBIT 3

New Polymer for Intra-Abdominal Meshes—PVDF Copolymer

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Abstract: ***Purpose:*** **Full tissue integration without adhesion formation is still a challenge for intra-abdominal mesh materials. Purpose of this study was to investigate the adhesive potential and fibrocollagenous ingrowth of a polymer blend of polyvinylidene fluoride and hexafluorpropylene (co-PVDF), an established suture material in vascular surgery, when placed as a mesh in the intra-abdominal position. The results were compared with a matching polypropylene (PP) mesh.** ***Methods:*** **In an established rabbit model, mesh implantation was performed by laparoscopy in the intraperitoneal onlay mesh technique. After 7, 21, and 90 days the degree of adhesion formation, foreign body reaction, bridging, and shrinkage of mesh area were investigated.** ***Results:*** **In the early phase after 7 and 21 days we found significantly more adhesions for PP, but no differences after 90 days. Analysis of tissue reaction showed a significantly lower fibrotic reaction for co-PVDF. The degree of shrinkage revealed no significant difference.** ***Conclusion:*** **Large-pore PP and co-PVDF-meshes showed comparable good results in the intra-abdominal position, with a reduced inflammatory tissue reaction for co-PVDF. Large pore meshes should be considered an alternative for the development of intraperitoneal onlay meshes.** © 2008 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 87B: 321–328, 2008

Keywords: IPOM; coPVDF; polypropylene; mesh; adhesion

INTRODUCTION

Although the preconditions for an ideal prosthesis in hernia surgery are well known today, the mesh that fits all requirements has yet to be found. In particular, this is true for the application of meshes in the abdominal cavity.

On the one hand we need a fibrotic reaction to the prosthesis for tissue ingrowth and attachment to the peritoneal layer of the abdominal wall. On the other hand, adhesions should be avoided to prevent bowel obstruction or fistula formation. To achieve these preconditions there have been developed several variations as an alternative to the film-like nonporous expanded polytetrafluorethylene (ePTFE) meshes. Most of the meshes used for hernia repair are constructed of polypropylene (PP), a polymer known for its initial inflammatory and consecutive fibrotic reaction. To prevent any direct contact of the PP to the bowels, the main principle was the addition of protective barriers. Beside autologous tissue such as omentum, these barriers can be of resorbable material such as hyaluronic acid, collagen, or carboxymethylcellulose or of nonresorbable material such as a layer of ePTFE. However, so far none of the available prosthesis fulfils all needs. In particular, any damage to the protective layer may permit adhesions due to the inherent inflammatory power of the polymer. Furthermore, the use of film-like materials reduces the elasticity of meshes, desired for improved adjustment to the physiology of the abdominal wall.

Polyvinylidenfluorid may be regarded as an alternative polymer for intraperitoneal onlay meshes (IPOM). It has been used as a suture material in vascular surgery for years, has shown superior textile properties, permits porous constructions, and has been proven to induce less inflammatory reaction.[1] Thus, we investigated a blend of polyvinylidene fluoride and hexafluorpropylene (co-PVDF) mesh in an IPOM rabbit model in comparison with a PP mesh. In a previous study, we have investigated the influence of different pore size of PP meshes, revealing significant more

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TABLE I. Textile Properties of the Co-PVDF and PP Mesh

Properties	Co-PVDF	PP
Filament	Monofilament	Monofilament
Pore size (mm^2)	8.29	9.1
Filament size (mils)	3.5	3.5
Weight (g/m^2)	52.3	24.1

adhesions and foreign body reaction for small pore meshes (pore size 0.6 mm),[2,3] To investigate and compare the impact of the polymer itself, we used meshes both made of monofilament strand and identical pore size (3.5 mm).

MATERIALS AND METHODS

PVDF copolymer with the molecular formula -$(CH_2$-$CF_2)$n- and -$(CF(CF_3)$-$CF_2)_x$-$(CH_2$-$CF_2)_y$- is composed in equal shares of a polymer blend of polyvinylidine fluoride (PVDF, Solef 1008, Solvay) and PVDF copolymer (95% PVDF; Solef 1008, Solvay) and 5% hexafluoride propylene (Solef 11010, Solvay). The homopolymer and the copolymer are blended in a double screw extruder, than spinned into fibers followed by drawing with a high drawing ratio.[4–7] In comparison with plain PVDF the blending of PVDF with hexafluorpropylene permits less stiffness and increased elasticity leading to higher elongation at break. Other parameters such as long-time stability and degradation remain unchanged.

The mesh samples were produced on a crochet machine (Müller, Switzerland). The open pore construction was built by an open pillar stitch in the wrap system and a patterned laying-in movement of a second thread. The second mesh is a modification of a commonly used PP mesh (Prolene®, Ethicon). Both meshes were made of a monofilament strand, filament size of 3.5 mil, with almost the same pore size of 3.5 mm, differing only in polymer type (Table I and Figure 1a,b). The pore size of meshes is given by the maximal distance within a pore,

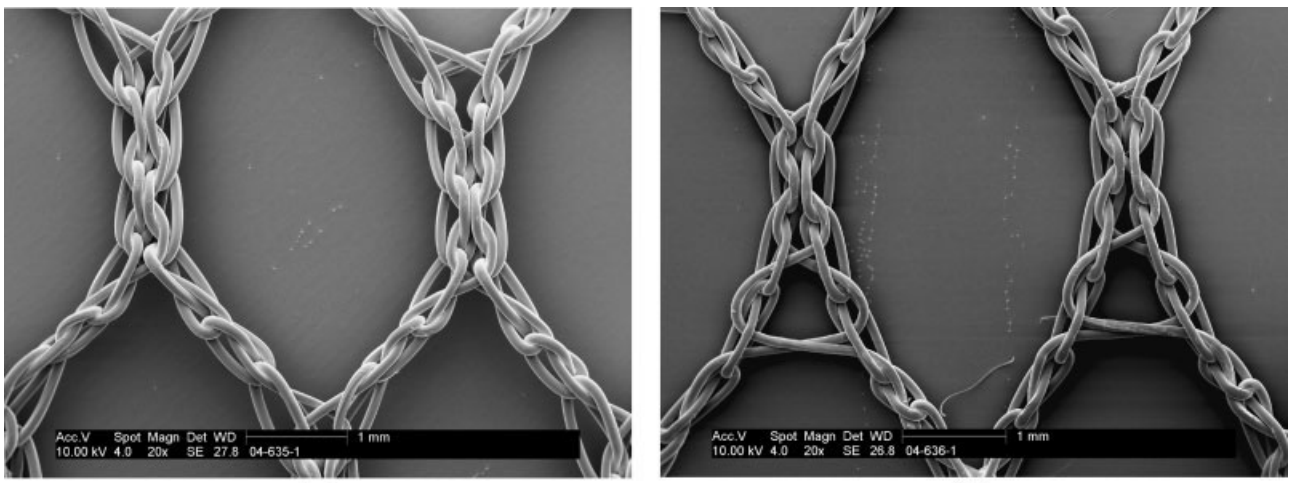
Surgical Procedure

A total of 36 adult female Chinchilla rabbits were randomly divided into six groups, six animals each. The animals were kept in single cages under standard conditions, with unrestricted access to a balanced pellet diet and water, according to the Rules of the Deutsche Tierschutzgesetz (AZ 23.203.2-AC 18,14/00) and to the National Institute of Health guidelines for the use of laboratory animals. Before surgery, the rabbits were quarantined for at least 7 days and food was deprived for 12 h before surgery.

The surgical procedures were performed under sterile conditions and general anesthesia by intravenous administration of ketamine (Ketamin 10%, Sanofi-Ceva, Düsseldorf, Germany) and xylazine (Rompun 2%, Bayer, Leverkusen, Germany).

The rabbit-IPOM model used in this study is an established, standardized setup to investigate the material induced reactions of biomaterials within the abdominal cavity. In contrary to adhesion model, were bowel is abraided, this model avoids any bowel manipulation to prevent further influence by tissue trauma.

After shaving and skin asepsis, laparoscopy was performed using a method similar to standard clinical practice. After creating a pneumoperitoneum three cannula were placed suprapubically on both sides of the lower abdomen. The meshes, with a standardized size of 5 × 6 cm^2, were taken into the abdominal cavity and fixed to the parietal peritoneum by an endoscopic stapler (Endopath®-Ethicon) with six staplers, one for each corner and one in the middle of the longer sides (Figures 2 and 3). After closing the cannula-fascia-defects, skin closure was obtained by single stitch absorbable suture (Vicryl® 3-0; Ethicon) and sterile



(a) (b)

Figure 1. a) EM—picture of the polyvinylidene fluoride and hexafluorpropylene mesh (PVDF-copolymer) b) EM—picture of the polypropylene mesh (PP).

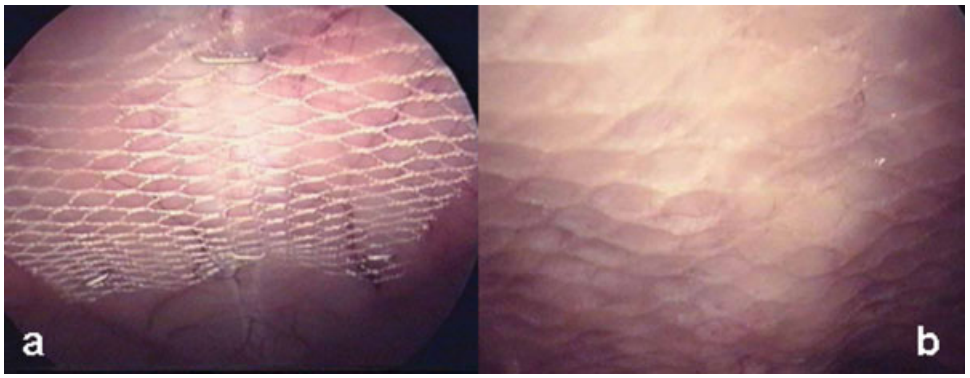


Figure 2. Laparoscopic view after implantation of PP-mesh with stapler fixation (a) day 1 and (b) day 90. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

wound spray. The animals were recovered from their anesthetic and maintained in standard condition. No antibiotic treatment was given before or during the experiment.

Adhesion Assessment

The intervals of investigation were 7, 21, and 90 days. In a final narcosis with an overdose of pentobarbital sodium a control laparoscopy was performed for clinical evaluation of the adhesion formation. The measurement of adhesion area was done after postmortem laparotomy via an U-shaped incision with its basis in the lower abdomen. Applying the mean adhesion score the degree and severity of adhesion formation were graded for each animal.[8] After subtle dissection of the adhesions the area was measured quantitatively by planimetry, using a digitizer board and calculation by custom-made software on a personal computer, expressed in square centimeter.

Radiography

The indirect visualization of meshes by the position of the fixation staplers in the abdominal wall *in vivo* was described by Amid in 1997.[4] Staplers made of titanium are radiological visible. After mesh implantation the animals are placed with their legs bend backwards, their abdomen pressed onto the x-ray table, to provide a plane contact. To allow a reproducible measurement a grid-iron scale is placed underneath. Radiography is performed and the area circumscribed within the four corner staplers is measured. Before planned explantation after 90 days a second radiography is taken. The degree of mesh area shrinkage, calculated by the comparison of the mesh area after implantation with the mesh area after 90 days before explantation, is given in percentage (%) (Figure 4).

Morphological Study

After mesh explantation tissue specimens were fixed in formaldehyde 10% and embedded in paraffin. Sections of 3 μm were stained with hematoxylin and eosin (H&E).

The foreign body reaction was measured by the diameter of granuloma formation around the mesh fiber. Thereby the inflammatory response, represented by the inner granuloma ring of macrophages, and the connective tissue induction, represented by the outer granuloma ring of fibrocytes, can be differentiated.[5] Per sample five granulomas were captured with a digital camera (400×, Olympus C3030, HH, Germany). With the help of a digital image analyzing software (Image-Pro Plus, Media Cybernetics, Silver Spring, MD) separate measurements of four quadrants per sample were taken.

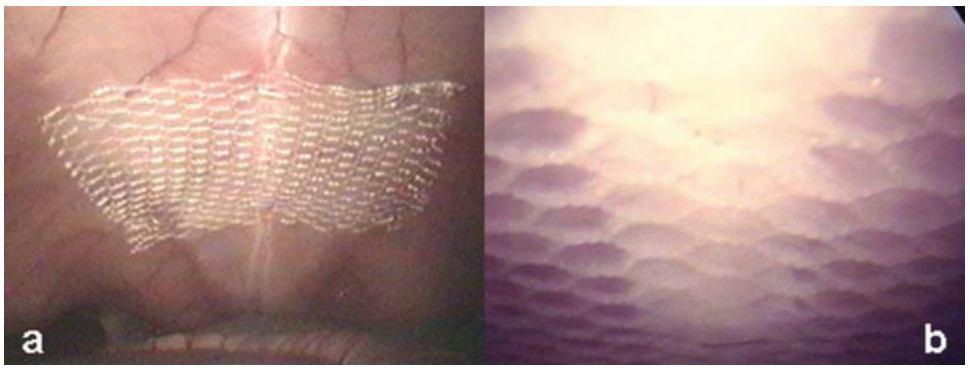


Figure 3. Laparoscopic view after implantation of co-PVDF-mesh with stapler fixation (a) day 1 and (b) day 90. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

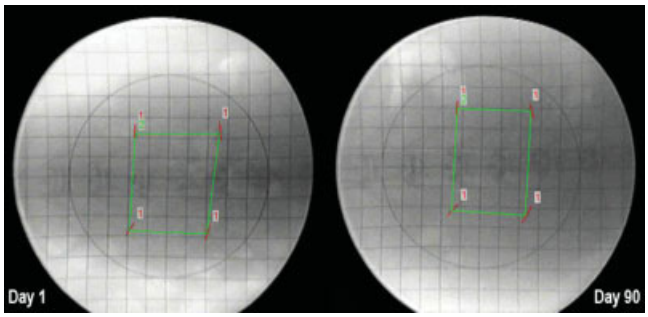


Figure 4. Technique of indirect measurement of mesh area shrinkage by radiography (PP day 1 and PP day 90). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

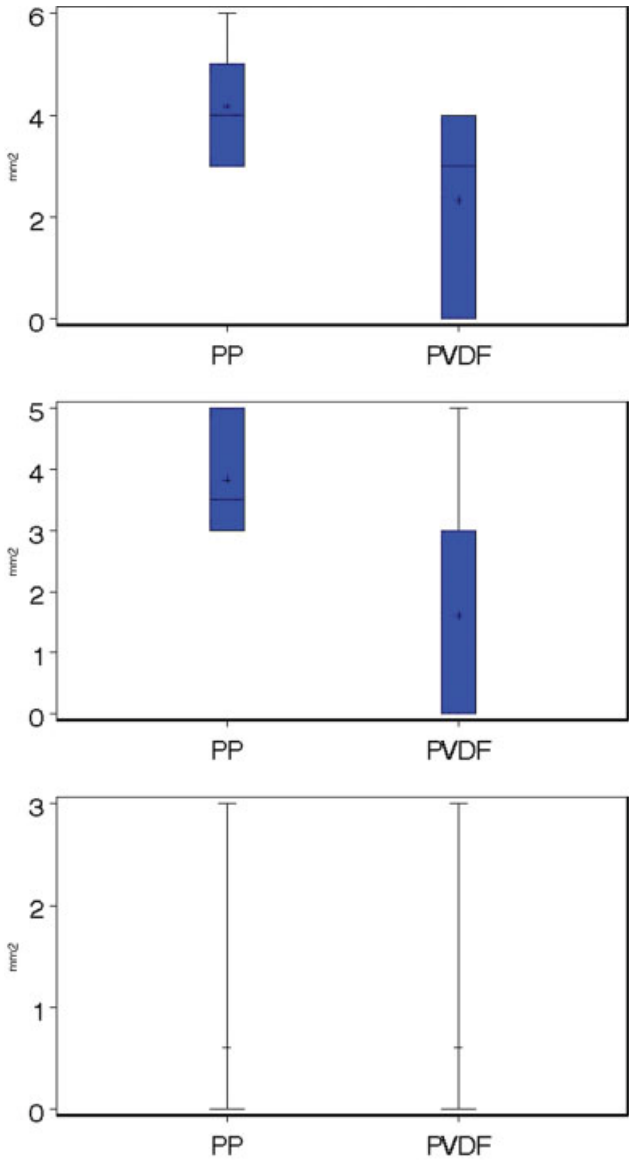


Figure 5. Adhesion score of PP and co-PVDF after 7, 21, and 90 days of implantation (boxplots). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Bridging

Depending on the distance between two neighboring perifilamental granulomas, a fibrocollagenous fusion between these granulomas, so called scar bridging, can develop. For this investigation we used the same specimens that were stained with hematoxylin and eosin (H&E) for the granuloma measurements.

After 90 days we performed 25 measurements for each mesh. Parameter for the bridging is the absence of intraporous fatty tissue. As critical distance we selected the maximum distance between the filaments where no fatty tissue could be detected. Thereby, we could exclude that bridging scar tissue in case of large distances only resulted by the diagonal dissection with staining always very close to the filaments.

Statistics

The statistical analysis was carried out using SAS (The SAS System, Release 8.02; SAS Institute, Cary) All data are expressed as means standard deviation (SD). The adhesive potential of different mesh pore sizes on the adhesion

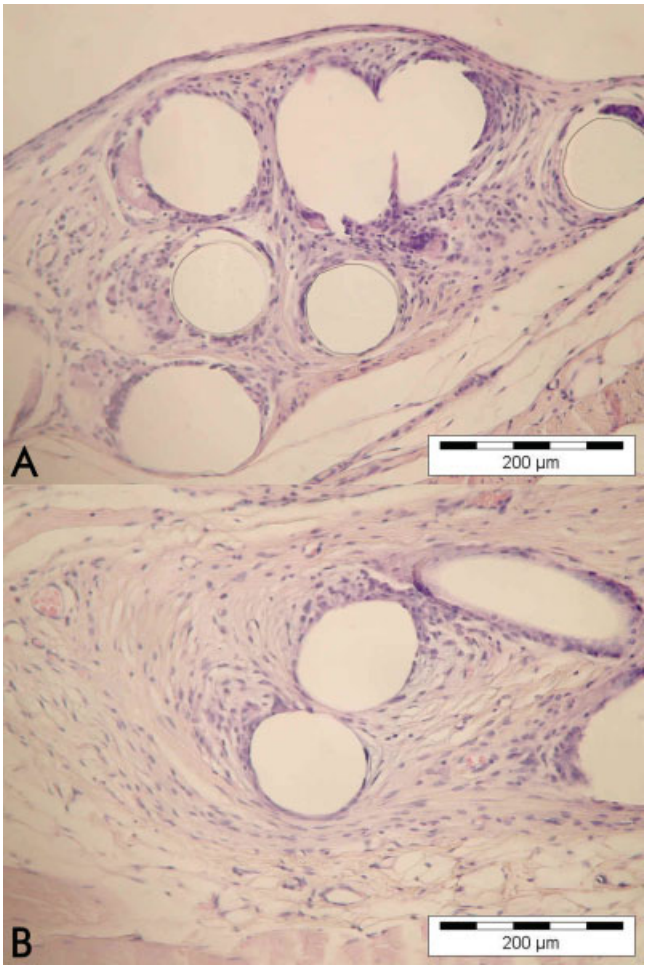


Figure 6. Foreign body granuloma after 90 days (a) co-PVDF and (b) PP. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II. Results of Adhesion Area and Score After 7, 21, and 90 Days

		Adhesion Area			Score		
Material	Interval	*N*	Mean	SD	*N*	Mean	SD
PP	7	6	479	344	6	4.2	1.3
	21	6	307	295	6	3.8	1.0
	90	5	5	11	5	0.6	1.3
Co-PVDF	7	6	92	85	6	2.3	1.9
	21	5	144	218	5	1.6	2.3
	90	5	13	28	5	0.6	1.3

PP, polypropylene; co-PVDF, polyvinylidene fluoride copolymer.

score as well as granuloma formation was evaluated by two factorial analysis of variance (ANOVA, factors MESH material and time) whereas shrinkage was evaluated using a single factorial ANOVA (level of significance: $p = 0.05$).

RESULTS

All animals survived the surgical procedure. In the follow-up three animals died before time of examination, one in the PP group and two in the co-PVDF group. The postmortem investigation showed no reason related to the operative procedure. Two died of pneumonia and one without detectable reason. All other animals showed an uneventful course. No animal showed signs of wound infection or fistula formation.

The control laparoscopy showed more and stronger adhesions in the animals with the PP prosthesis after 7 and 21 days.

After 90 days almost no adhesions could be detected for both materials.

Adhesions

The mean adhesion score is summarized in Table II and Figure 5. The overall adhesion score range from 0 to 11. It was highest in PP after 7 days (4.2, SD 1.3) compared with 2.3 (SD 1.9) for co-PVDF at the same time interval, and decreased over the investigation period to 0.6 (SD 1.3) for both materials after 90 days.

The mean prosthetic surface area covered by adhesion measured by planimetry underline the findings of the laparoscopy. In the PP group, we found 7 days after implantation a mean adhesion area of 479 mm^2 (SD 344), decreasing after 21 days to 307 mm^2 (SD 295) to a mean of 5 mm^2 (SD 11) after 90 days.

The mean adhesion area after implantation of a co-PVDF prosthesis was 92 mm^2 (SD 85) after 7 days, 144 mm^2 (SD 218) after 21 days, and 13 mm^2 (SD 28) after 90 days (Table II). Statistical analysis of the different materials at each investigational time point revealed significant difference at 7 days ($p < 0.01$).

Histology/Morphometry

Microscopically all mesh samples appeared well integrated into ingrowing tissues. Already after 7 days but in particular after 21 days the filaments were surrounded by typical foreign body granulomas with a fibrotic capsule. After 90 days any signs of acute inflammation widely disappeared, though there remained a cellular infiltrate around the filaments, with considerably more macrophages in case of PP compared with PVDF. The pores in between the filaments mainly were filled with fatty tissue, showing moderate scar formation mainly around the cellular infiltrate.

Measurements of mean sizes of the inner granuloma showed a mean size of 13.1 μm (SD 1.8) for PP 7 day after implantation, 10.2 μm (SD 3.1) for co-PVDF, respectively, being of significant difference ($p < 0.01$). The results after 21 and 90 days revealed almost consistence without any significance.

At all intervals the measurements of the outer granuloma revealed significant higher values for the PP meshes compared with the co-PVDF meshes, with a peak after 21 days (53.2 μm, SD 3.7 vs. 36.4 μm, SD 2.4; $p < 0.01$ at 7 days and $p < 0.01$ at 21 and 90 days, respectively).

The total granuloma size results in highest values after 21 days with 64.3 μm (SD 4.4) for PP and 48.9 μm (SD 2.7) for co-PVDF (Figure 6). All intervals exposed statistical significance ($p < 0.01$ at 7, 21 and 90 days) (Table III).

Shrinkage

The initial value of the radiographic marked mesh size was 1739 mm^2 (SD 128) for PP and 1890 mm^2 (SD 118) for co-PVDF, respectively. After 90 days the radiography showed a reduction of mesh size to 1635.9 mm^2 (SD 124) for PP, corresponding to a shrinkage of mesh area of 9.4%.

TABLE III. Diameters of Granuloma Formation (μm) With SD

		Inner Granuloma			Outer Granuloma			Total Granuloma		
Material	Interval	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
PP	7	6	13.1	1.8	6	37.7	6.5	6	50.8	8.2
	21	6	11.3	1.4	6	53.1	3.8	6	64.4	4.6
	90	5	10.6	0.9	5	45.8	6.1	5	56.4	6.4
Co-PVDF	7	6	10.2	3.1	6	29.7	5.5	6	39.9	8.3
	21	5	12.4	0.5	5	36.4	2.4	5	48.9	2.7
	90	5	12.3	0.8	5	31.7	2.8	5	44.0	3.4

PP, polypropylene; co-PVDF, polyvinylidene fluoride and hexafluorpropylene.

In the co-PVDF group there was a reduction of mesh size to 1753 mm^2 (SD 119), corresponding to a shrinkage of mesh area of 9.3%, revealing no statistical difference between the two materials.

Bridging

In the PP meshes we found 90 days after implantation always a persisting scar tissue below a filament distance of 1042 μm. Above this distance there was no granuloma bridging between the two filaments. In the co-PVDF meshes a bridging was always detected below a pore size of 630 μm.

DISCUSSION

Laparoscopical hernia repair has been proven to be advantageous in terms of a reduced surgical trauma and a faster recovery after surgery.[6,7,9] However, there is still a remaining problem of mesh material and its fixation.

Due to the growing number of laparoscopic procedures for incisional hernia repair the need of a prosthesis that allows an intra-abdominal placement without the risk of adhesion formation has become more important. Although some surgeons use PP meshes within the abdominal cavity particularly in laparoscopic incisional hernia repair, the implantation of this polymer with direct contact to the intestine remains controversial[10,11] because of its potential of formation of dense adhesions and enterocutaneous fistulas.[12] In a recently published retrospective analysis of reoperations after intra-abdominally versus preperitoneally PP mesh implantation, Halm et al. found more preoperative and postoperative complications when the mesh is placed intraperitoneally.[13]

The crucial problem is how to solve the balancing act of good tissue integration to the abdominal wall on the one side with no adhesion formation to the bowels on the other. One possible solution may be the use of a porous structure of a polymer with minimal inflammatory and fibrotic foreign body reaction.

PVDF has been shown to have an improved biocompatibility even in the early period. Furthermore it shows structured perifilamental tissue integration into a moderate scar. The molecular structure of co-PVDF resembles the structure of ePTFE. They differ in the amount of fluoride bonding to the carbon atom, where PVDF has fluoride bonding only to every second carbon molecule. Co-PVDF has been evaluated as suture material in cardiovascular surgery already for many years. *In vitro* testing revealed textile properties in respect to tensile strength, elongation, bending stiffness and surface, superior to common PP sutures.[14] Measurements of resistance to degradation by Laroche et al. revealed a preserved mechanical stability of 92.5% after 9 years of implantation.[15] For the construction of meshes with large pores the recommended tensile strength for the device requires thicker fibers. Because of the high stiffness of thick PP fibers, PVDF may be advantageous because fibers of this polymer reveal a higher elasticity and furthermore its higher tensile strength permits the use of thinner fibers to achieve a sufficient stability.

Comparing the textile parameters of the two meshes of this study they differ obviously in weight. Due to its higher specific density PVDF copolymer is more than twice as heavy as the equivalent PP mesh used in this study though the volume of both meshes are almost the same. In times of mesh classification into heavy and light weight meshes the PVDF mesh represents a heavy weight but large pore mesh. To evade further misconception we suggest future description and classification of meshes rather on the base of porosity and/or surface area.

It has been already shown that PP in large pore constructions causes less inflammatory reaction than in small pore meshes. This can be confirmed by the excellent results of the PP mesh used in this study after 90 days. In accordance the total granuloma size found was markedly less than reported with small pore PP meshes (64 μm vs. 106 μm).[3] However, within the early period there is a considerable inflammatory reaction.

At all intervals co-PVDF showed a significantly reduced inflammatory and fibrotic reaction compared with PP. This is indicated by a decreased size of the foreign body granuloma even after 90 days (49 μm). As a result of smaller granulomas and less fibrosis the fibrotic bridging between the filaments disappeared when the pore size exceed 630 μm for PVDF, whereas it requires pore sizes of >1000 μm in case of PP. Considering the identical thread size and surface the smaller bridging distance of co-PVDF indicates an improved biocompatibility. Furthermore, this finding permits the construction of meshes of smaller pores if PVDF is the basic polymer, offering more possibilities to adopt the textile structure to the physiological and surgical demands. In particular, the demands for laparoscopical use favors constructions where the limited size of the pores permits transparency but not too much flexibility, a purpose which is difficult to realize with large pore PP-mesh constructions due to its sometimes inappropriate floppiness.

The significant reduction of adhesions after 7 days in the PVDF group underlines the reduced inflammatory activation by this polymer, already at this early time point. However, in our study we found no significant difference in the adhesive potential between the two investigated meshes after 90 days. The disappearance of almost all adhesions after 90 days, even in the PP group, stresses the importance of large pores, which may exceed the importance of the polymer itself. It is in accordance with former studies that showed a close correlation of increased pore size and adhesion formation.[3]

The low cellular activation after 90 days in both groups with comparatively little scar formation may explain the little shrinkage of 10%. The investigation of the degree of shrinkage is not shrinkage of the biomaterial itself but

reduction of mesh area due to the physiological wound contraction. The extent of this process again is dependent on the biocompatibility of the implanted biomaterial and its parameters and is suspected to the extent of inflammation and fibrosis. Small pore PP meshes are known for their potential of shrinkage, with an area reduction of up to 40% within 6 months after implantation.[4,16] This phenomenon is well known from explanting mesh samples, which often appeared to be considerably shrunken, in particular known for plugs.

Furthermore, the radiological results are limited by the confinement to an only planar view that cannot provide an estimation of a possible bending of the mesh. However, during the X-ray examination the animals are pressed on the X-ray table with their legs bend backwards to achieve a flat position of the abdominal wall. The results do not pretend do give the absolute mesh size but allow a comparison of meshes investigated in the same way. Due to the similar textile parameters of the two investigated meshes and their almost similar extent of inflammation after 90 days it is not surprising that the degree of mesh area shrinkage is low and almost identical.

The current available materials for intra-abdominal placement have some disadvantages: ePTFE has more a foil-like structure that hinders a perifilamental fibrocollagenous ingrowth and therefore needs permanent fixation. In case of infection it usually necessitates mesh explantation. Last not least it is quite expensive. Porous meshes of PP or polyester probably need less fixation but are more often associated with adhesion formation when in contact with intestine. Therefore they are combined with different absorbable barriers to reduce their adhesive potential. Great efforts are undertaken to solve the problem: lining or coating of nonabsorbable meshes with different materials such as resorbable hyaluronic acid, collagen, and carboxymethylcellulose, or nonresorbable materials, for example, an extra layer of ePTFE, adding another generation of meshes to the surgeon's armamentarium. These composites and compounds try to stimulate and facilitate a fibrocollagenous ingrowth to the side of the parietal peritoneum and remain antiadhesive on the visceral side. In several animal studies the advantage of different absorbable barriers could be demonstrated, though no material so far seems to be able to prevent adhesion formation completely.[17–20] Furthermore the combination of two or more different materials and/or structures changes the textile and biological properties. Certainly, this results in an increase of foreign material and most often lead to a reduction of mesh elasticity.

Correspondingly, the development of porous mesh structures of a polymer that does not need an additional barrier to avoid adhesion formation seems to be promising. Further studies have to clarify whether a structure can be realized that finds a balance between preventing intra-abdominal scar formation but sufficient fibrocollagenous integration into the abdominal wall, and a balance between porosity and sufficient stability, correspondingly.

CONCLUSION

The results of this experimental study reveal favorable results for both investigated large pore meshes. Co-PVDF seems to be promising for the construction of porous meshes without the need of an additional barrier substance. However, it appears that beside the polymer itself, the textile structure, such as pore size and surface area, have a great impact on the biocompatibility. It has to be verified, whether the incorporation is strong enough to place it even without any permanent fixation. It cannot be excluded, that regarding the conflicting goals of good integration to one side and no integration to the other any solution has to be a compromise.

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